AUDITORY EVOKED RESPONSE AND AWARENESS: A STUDY IN VOLUNTEERS AT SUB-MAC CONCENTRATIONS OF ISOFLURANE


SUMMARY

We have investigated the relationship between the auditory evoked response (AER) and simple tests of conscious awareness at four end-expiratory concentrations (0.0, 0.1, 0.2 and 0.4 MAC) of isoflurane in oxygen in each of eight anaesthetist volunteers, in random order, at least 1 week apart. The early cortical AER was recorded from electrodes at the vertex and inion. Amplitudes of the waves Pa, Nb and Pc and latencies of the waves Na, Pa, Nb, Pb and Nc were measured. All the AER variables were highly significantly related to end-expiratory anaesthetic concentration. Amplitudes decreased and latencies increased progressively with increasing anaesthetic concentration. The AER variables were also highly significantly related to the level of response. Amplitudes were greatest and the latencies shortest when there was full response to command. (Nb latency increased from 47.5 to 54.5 ms between partial and no response.) The close correlation between the effects of concentration and level of response, and between concentration and the AER implied that it was difficult to demonstrate those changes in the AER which specifically relate to changes in response. At 0.2 MAC, however, which was the concentration at which all subjects showed some deficit, the response to a shock word was distinguished clearly by Nb latency. In eight of 24 possible comparisons (eight AER variables and three types of psychological test) the AER fitted the response more closely than concentration.

KEY WORDS


The auditory evoked response (AER) has been shown to change in response to increasing concentrations of anaesthetic agent [1,2]. In particular, the early cortical component has been shown, in previous studies, to change in a similar manner with increases in blood or end-expiratory concentration of a wide range of anaesthetic agents, both i.v. and volatile [1,3,4]. At low concentrations of anaesthetic, characteristic changes in the early cortical AER also reflect the change between wakefulness (responding to command) and light anaesthesia (no response) [5]. These last experiments, performed on paralysed surgical patients, using the isolated arm technique before the start of surgery, demonstrated that a change in the latency of the early cortical AER wave Nb, characterized the transition from responsive to anaesthetized. However, there were several equivocal responses, and the ethical and practical problems associated with extending these studies in patients led to the conclusion that further studies should be conducted in volunteers.

Preliminary studies, and previous experience, suggested that for isoflurane, the transition between wakefulness and light anaesthesia occurred at less than 0.4 MAC. A study was performed therefore on volunteers breathing stable end-expiratory concentrations of 0.1, 0.2 and 0.4 MAC and 100% oxygen (control) on separate occasions. The results of test studies, relating anaesthetic concentration to psychological tests of response to command, memory tasks and clinical signs of light anaesthesia, have been reported previously [6]. This paper reports the relationship of these findings to the AER.

SUBJECTS AND METHODS

The study was approved by the hospital Ethics Committee. Eight anaesthetist volunteers breathed isoflurane vaporized in oxygen. Each was allocated randomly to receive either 100% oxygen, or 0.1, 0.2 or 0.4 MAC of isoflurane (end-expiratory) in oxygen at sessions separated by at least 1 week; 1 MAC = 1.15% [7]. No correction was made for the age of the subjects. The end-expiratory concentrations were maintained by the technique of overpressure. The
inspired concentration of isoflurane was adjusted manually to hold the end-expiratory concentration at the target level.

The test sessions were divided into six periods, the first breathing 100% oxygen, and subsequent periods breathing the test mixture with the subjects resting, given commands, given word lists, again resting, and finally breathing 100% oxygen, respectively (table I). Subjects and observers were blinded to the target composition of the end-expiratory gas, and the controls were given a trace smell of isoflurane to blind them [6].

Psychological tests were of three types. The level of consciousness was assessed at the end of the second period when the end-tidal isoflurane concentration had been stable for at least 10 min (table I). The subject was asked loudly to open his eyes and close them. If there was no response the eyelash reflex was tested. In the third period, commands to raise a finger were presented. During the fourth period the subject heard 30 words. He was again asked to signal by raising a finger that he had heard each word. Included in each word list was a “shock” word (usually amusing) and any additional response of the subject was noted. The subjects were tested for memory of words and events 1 h after the anaesthetic.

**Table I. Experimental procedure**

<table>
<thead>
<tr>
<th>Period</th>
<th>Activity</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breathing 100% oxygen</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Test gas: resting then clinical assessment of depth</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Test gas: given commands</td>
<td>2.75</td>
</tr>
<tr>
<td>4</td>
<td>Test gas: hears words</td>
<td>2.75</td>
</tr>
<tr>
<td>5</td>
<td>Test gas: resting</td>
<td>5.5</td>
</tr>
<tr>
<td>6</td>
<td>Breathing 100% oxygen</td>
<td>Until awake</td>
</tr>
</tbody>
</table>

**AER recording**

In all subjects the EEG was recorded unfiltered on an FM tape recorder using a purpose built, optically isolated, low noise amplifier, from silver-silver chloride electrodes on the vertex and inion, with an indifferent electrode placed over the right sternoclavicular joint. The contact of the electrodes was checked to ensure that inter-electrode resistances were less than 5 kΩ. Rarefaction clicks were presented at a rate of 6 s⁻¹ to both ears using Cadwell insert headphones which had been found by experiment to be more acceptable to awake subjects than the Telephonics TDH 39P headphones used in previous patient studies. Commands and words were fed from a cassette player into the same headphones using an audio mixing system, such that the intensity of the stimulation clicks was unaffected. The clicks were recorded separately on the same tape. At each recording, a calibration signal was put onto the tape recorder and the resulting signal used to set the gain on playback.

**AER analysis**

The FM tapes were played back at 16 times real time. The EEG signal was analogue filtered with an effective real-time band width of 25-500 Hz. The filtered EEG signal and the trigger stimulus signal were fed into a Loughborough Sound Images digital signal processing (DSP) card, resident within an IBM AT PC. To reduce noise levels further, digital filtering was performed on the final averages with a high-pass filter of greater than 30 Hz and a low-pass filter of 125 Hz. The high-pass filter was of the linear phase finite impulse response type and the low-pass filter was a Butterworth infinite impulse response filter which was applied to the data once in each direction to nullify any phase changes.

The evoked response was extracted from the background noise (mainly EEG and EMG) by signal averaging. To reduce the influence of artefacts a weighted averaging technique was used in which each sweep was weighted by a factor that was inversely proportional to the noise power in that sweep, before being added to the accumulating sum. Thus noisy sweeps contributed less to the averages than “quieter” sweeps. A total of 1024 sweeps were averaged for statistical analysis. This represents the last 2.8 min of periods 1, 2 and 5 and the whole of periods 3 and 4. On occasions, in order to differentiate between short consecutive periods when the subjects were responding intermittently, a smaller number of sweeps was averaged.

Amplitudes and latencies were measured by hand-on printed plots. The amplitude of a peak is defined as the height of a vertical dropped onto a line drawn between adjacent troughs.

**Statistical analysis**

The order of presentation of the four treatments and four word lists for each of the subjects was randomized using a Greco-Latin square. The desired anaesthetic concentration was communicated only to the operator of the vaporizer/gas analyser. The AER data were log₁₀ transformed and analysed using ANOVA in the Genstat V, release 1.3 program installed on a Sun computer. The analyses were: AER variables vs concentration; and AER variables vs responses to command which were either full (all words and commands responded to), partial (some words and commands responded to) or absent in each of the three periods 2–4 (table I). Results are expressed as the geometric mean and 95% confidence intervals. To differentiate between the relationship of the AER variables to concentration, and response to command, the residual mean squares from each of the analyses were compared for the eight variables and the three test periods (2–4).

**RESULTS**

The responses to commands and words at the various MAC are summarized in table II and have also been discussed previously [6]. At 0 MAC (100% oxygen) there was full response to commands and words. At 0.1 MAC small deficits in the response were seen in subjects 1, 2, 4 and 8. Differences in the AER between 0 and 0.1 MAC were small and not restricted to the subjects showing deficits. The relationship between the AER variables and MAC is shown in table III.
At 0.4 MAC there were no responses to commands or words by any subject. (In subject 8, the session had to be discontinued because he showed hyper-excitation.) When the AER at 0 and 0.1 MAC were considered together and compared with those at 0.4 MAC, there were clear differences in all subjects, as were the differences at 0.4 MAC from the controls (100% oxygen, period 1) in the same session.

At 0.2 MAC all subjects showed deficits in their response to commands or words, and the waveforms of the AER often resembled those at 0 and 0.1 MAC and at other times those at 0.4 MAC. However, the deficits in the responses and the resemblance of the AER to those at 0.4 MAC were not obviously related. For example, subjects 1 and 3, whose data are shown in figure 1, showed no response to simple commands and words at 0.2 MAC although they had opened their eyes previously when asked to do so. In the case of subject 1, the 0.2 MAC AER resembles the 0.1 MAC AER rather than that at 0.4 MAC. In contrast, the 0.2 MAC AER of subject 3 resembles the 0.4 MAC AER rather than that at 0.1 MAC.

At 0.2 MAC subject 5 showed no response to the words, although he responded intermittently to commands. His AER were not different for the command and word periods (fig. 2).

Seven subjects (1, 2, 4–8) showed intermittent responses to words, commands or both. However, only four of these (subject 1 at 0.1 MAC, and subjects 5–7 at 0.2 MAC) had sufficiently long consecutive periods where there was lack of response (at least 20 s) to be able to test if there was any change in AER. Subjects 1, 5 and 6 showed little difference in the AER in the two situations, whereas the latencies of subject 7 were greater when there was no response compared with when there was. The data from subjects 5 and 7 are shown in figure 3 as examples.

Inspection of the individual waveforms showed clear differences as the MAC varied between 0 and 0.4 MAC, and between full response and no response situations. It was difficult to tell if the AER changes were related more closely to changes in concentration or changes in the level of the response. An example where there was a clear distinction was the response to the shock word at 0.2 MAC. There was a clear distinction in Nb latency between those subjects who responded to the shock word and those who did not (fig. 4), and those who remembered the shock word and those who did not.

**Statistical analysis**

Table III shows changes in the AER related to
Subject 1  Subject 3

0.1 MAC
0.2 MAC
0.4 MAC

FIG. 1. Averaged early cortical AER (1024 sweeps) of two subjects during the words session. Neither subject showed any response to commands or words at 0.2 MAC of isoflurane. For subject 1 the 0.2 MAC AER appeared more like that at 0.1 MAC than that at 0.4 MAC. For subject 3 the converse was true.

Subject 5  Subject 7

0.5 uV

FIG. 2. Averaged cortical AER (1024 sweeps) of subject 5 at 0.2 MAC during the commands (---) and words (----) session. This subject responded intermittently to the commands but not at all to the words.

FIG. 3. Averaged AER of subjects who showed intermittent responses to commands (subject 5) or words (subject 7). Nb latency appears later where there is no response to command in both cases. The traces represent short epochs of 165 sweeps (subject 5) and 291 sweeps (subject 7) when the subjects were not responding (-----) and of 486 sweeps (subject 5) and 434 sweeps (subject 7) when they were responding (-----).

FIG. 4. Nb latencies at 0.2 MAC of the eight subjects at the time when they were subjected to the shock word. Response to, and memory of, the word is shown for each subject.

anaesthetic concentration which were highly significant for all the variables measured. The changes were greatest between 0.2 and 0.4 MAC. The amplitudes decreased and the latencies showed progressive increases with increasing concentration. No difference could be found between periods 2 and 5, in which there was no stimulation (i.e. speaking to the subject) during the recordings, and periods 3 and 4 (the commands and words). That is, there was no effect of stimulation, or any difference between the two periods (3, commands and 4, words). The difference between 100% oxygen and anaesthetic periods (2–5) varied significantly with concentration, and at greater concentrations this effect was more pronounced.
Tables IV–VI show the relationship of the changes in the AER variables to the levels of response (complete, partial and none) to the various commands. Again there was a highly significant change for most of the AER variables: latency increased, amplitude decreased.

Correlations with changes in end-expiratory concentration (table III) tended to be better than with behavioural response (table IV). In eight of the 24 possible comparisons (eight AER variables in three test periods), the residual mean square was smaller using response compared with using concentration, that is, the AER fitted more closely to the actual response than to concentration. These were Pa and Nb latency in period 2, Pb latency in all periods (2–4), Nc latency in periods 3 and 4, and Pc amplitude in period 3.

**DISCUSSION**

This study had three aims: first, to demonstrate the changes in the AER as a patient passes from the awake to the lightly anaesthetized state; second, to establish the relationship between the AER waveform and conscious awareness; and third, to confirm previous findings in anaesthetized patients [5]. Because of the intangible nature of anaesthesia, it is essential to define the terms which categorize the state of the subject. The most useful definitions of anaesthesia have been reviewed by Prys-Roberts [8].
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who dismissed the concept of depth of anaesthesia as incorrect, but rather categorized levels of anaesthesia in terms of the response of the subject to noxious stimuli and the modification by anaesthetics. In this study, we considered only one level of anaesthesia, namely hypnosis or drug-induced sleep in which the subject loses conscious awareness, which is the loss of response to command and memory of that command.

In the design of this study, it was assumed that there would be a progression of stages in the loss of conscious awareness, defined by measurable endpoints, through which the subject passed as the concentration of the anaesthetic was increased. The endpoints were the loss of memory of bland words, memory of shock words, memory of hearing commands and loss of response to commands and of the eyelash reflex, and these were discriminated by the psychological tests reported previously [6].

The overall effect of increasing the concentration of isoflurane was an abrupt and profound change in the subject’s state such that fine gradations were not always seen and the loss of conscious awareness tended to be all-or-none and occurred within the range 0.2 to 0.4 MAC. For the study as a whole, it was difficult to separate the small gradations in the behavioural changes and their effect on the AER from the profound effect of concentration. The problem of interpretation in this type of study is that at the level of sedation produced by 0.2 MAC where the most interesting changes occurred, the degree of attention necessary for the subject to perform the tests may be severely impaired yet the level of conscious awareness is clearly enough to permit a positive response to a more stimulating word. Many subjects reported having a “couldn’t care less” attitude to compliance with the testing and this may explain the observation shown in figure 4, where one subject remembered the shock word but did not respond to it at the time. In addition, a drawback in the use of the AER to observe subjects whose CNS state is not stable, is the time taken, using current technology, to build up an average. Much of the difficulty in the interpretation of the AER when a subject is changing back and forth from one level of consciousness to another (fig. 3), may be because the averages are likely to be composites of more than one population of response.

The failure to discriminate effectively more subtle changes in the AER in relation to the progressive loss of mental faculties with deepening anaesthesia is also a function of the relative potency of isoflurane as a hypnotic, and the abrupt transition with increasing concentration from the awake to the anaesthetized state. The use of a less potent agent, such as nitrous oxide, may allow greater discrimination. At 0.2 MAC, however, there was sufficient individual variation in response for a distinction to be seen in some of the subjects. This is demonstrated best in subject 7 (fig. 3), for whom there was a distinct increase in Nb latency associated with loss of response. This is associated with a change in the cortical waves from a three- to a two-wave pattern, a change which has been demonstrated previously to distinguish response from no response in surgical patients tested using the isolated arm technique [5].

Taking the group data as a whole, highly significant changes in all the measured AER variables reflected the effect of increasing the concentration from 0.2 to 0.4 MAC (table III), and corresponded with the change from a three- to a two-wave pattern. Nb latency increased from a mean of 46.7 to 53.9 ms. In a previous study [5], an Nb latency of 44.5 ms was the threshold above which a three-wave became a two-wave pattern. This change in the AER reflected the ability to respond or not to command. At 0.2 MAC there were clear differences in the AER during the word period depending on whether or not the subjects did or did not respond to, or remember, the shock word and this is demonstrated best by the differences in Nb latency seen in figure 4.

Differences in the methods in this study could account for the longer Nb latencies in both the awake

### Table VI: Mean (95% confidence intervals) AER during words assessment in period 4. Response: full = finger raising on hearing all 30 words; partial = finger raising when < 30. P value from comparison of all three responses (analysis of variance)

<table>
<thead>
<tr>
<th>AER</th>
<th>Full (n = 16)</th>
<th>Partial (n = 5)</th>
<th>None (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nb</td>
<td>(21.9)</td>
<td>(37.3)</td>
<td>(54.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pb</td>
<td>(45.8)</td>
<td>(54.3)</td>
<td>(54.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nc</td>
<td>(77.8)</td>
<td>(92.3)</td>
<td>(92.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na</td>
<td>(0.30-0.38)</td>
<td>(0.38-0.49)</td>
<td>(0.38-0.49)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pk</td>
<td>(0.23-0.45)</td>
<td>(0.29-0.49)</td>
<td>(0.29-0.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pc</td>
<td>(0.25-0.35)</td>
<td>(0.29-0.49)</td>
<td>(0.29-0.49)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
and anaesthetized states. First, insert headphones were used such that the electrical transducer was some distance away from the ear, and acoustically coupled. We followed the manufacturer's instructions and allowed for a delay of 1 ms, the time taken for the sound to travel. Quieter clicks may also have affected Nb latency. The same headphones were used to transmit the commands and words from magnetic tape and we do not know what effect, if any, this arrangement would have on the response. No changes were detected in the AER with 100% oxygen when the psychological testing was in progress, but conversely the click stimuli may have distracted the subject and diminished the psychological scores. There is no way of checking this, but experience has not demonstrated any problem in communication with either awake patients or volunteers when eliciting the AER. In contrast with previous studies, the entire recording and analysis system was purpose built and incorporated weighted averaging and digital filtering. Standard analogue filters were applied to allow comparability with other AER data and the digital filters, while giving considerable cosmetic improvement to the appearance of the AER, were the same in every experiment and helped greatly the analysis of results reducing, for example, the degree of EMG contamination seen in awake subjects.

The use of the early cortical waves in the study of cognitive function requires justification. Pa and Nb are believed to emanate from the primary auditory cortex [9,10] and demonstrate registration of a supramaximal sound stimulation. The changes in Pa/Nb with anaesthesia, therefore, reflect declining activity at a rather low level of cortical function, but are useful because they take place over the clinical range of concentrations of anaesthetic agents. Later waves (P1 (Pb)) begin to reflect processing and are affected, for example, by attention [11,12]. However, if it can be accepted that anaesthesia is a depression of the higher levels of cerebral cortical function, then the early cortical AER is a method of applying a stimulus to a sample of the cortex and observing the effect of anaesthetic drugs. By implication, the anaesthetics may have more effect on levels of consciousness than on other functions because that cortical activity is the most complex. To study the more sophisticated aspects of cortical function associated with the transition between awake and anaesthetized, even later waves of the AER have been used, in particular, event-related potentials such as the P300. These responses are variable and depend on the attention of the individual but, when present, allow investigation at a higher level of processing. The P300 has been used [13] to demonstrate loss of memory with increasing nitrous oxide concentration (greater than 50%) in subjects who were still performing tasks. A dose-dependent reduction of P300 amplitude has been demonstrated with increasing concentration of nitrous oxide [14] which correlated with a reduction in psychomotor performance, but in that study, the concentration was not increased to the point of anaesthesia. However, these late cortical waves are abolished by clinical concentrations of the anaesthetics and indeed by sedative agents. Clearly, techniques which study the processes of consciousness can be used to monitor awareness during surgery [15], but in this study the changes in the early cortical AER are part of a spectrum which includes clinical anaesthesia and therefore have more general application in the operating theatre.

Osterhammel, Shallop and Terkildsen [16] and Erwin and Buchwald [17] have demonstrated the effect of sleep on the early cortical AER. The AER findings were similar to those seen in this study with the disappearance during slow wave sleep of P1 (Pb) and the consequent increase in Nb latency. This corresponds with the transition from the three- to two-wave pattern in the 20–100 ms window that we have described [5]. Erwin and Buchwald observed the reappearance of P1 during REM sleep and postulated that it was associated with reticular activating system activity and arousal. There was one significant and interesting difference from our results in light anaesthesia. In the asleep patients, Pa latency changed little from the awake value; in the anaesthetized subjects, there was a large and significant increase in Pa latency which corresponded with the transition from partial response to not responding (table VI). It is therefore possible to use the AER to distinguish between light anaesthesia and sleep.

We have not tested if there is a mechanism of arousal to conscious awareness from light anaesthesia (as indicated by the AER) by the application of a painful stimulus. This has yet to be done. However, the early cortical AER, when used to assess anaesthetic depth, is clearly able to demonstrate potential awareness. This is best illustrated in table VI where large significant changes in the latencies of Pa and Nb accompany the transition from partial to no response. In practical terms it is of little interest to the anaesthetist to distinguish between partial response and full awareness: neither is acceptable. The patterns seen when the subjects were aware, albeit sometimes intermittently, were very different from those seen during clinical anaesthesia [1–4] and when there was no response. Our findings confirm our view that the early cortical AER can be used as a clinical monitor.

REFERENCES


